REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 52, 55, 57-60, 74, 75, 78-100 are in this Application. Claims 61-73 have been withdrawn from consideration. Claims 52, 55, 57-60, 74, 75, 78-100 have been rejected under 35 U.S.C. § 103. New claim 101 has been added herewith.

Amendments To The Claims

35 U.S.C. § 103 Rejections

Thomson, Harper, US. Pat. No. 7,390, 659 and Elsea

The Examiner rejected claims 52, 55, 58-60, 74, 75, 78-80, 85, 86, 88-94, 99 and 100 under 35 U.S.C. 103(a) as being unpatentable over Thomson et al., 1998, in view of Harper et al., 1996 (J. of Assisted Reproduction and Genetics, 13:90-95) in further view of US. Pat. No. 7,390,659 (cited previously) and Elsea et al., 2002. The Examiner states that Thomson teach hESCs from IVF embryos and teach that genetic modifications could be produced in ES cells for reducing or combating immune rejection; production of cell lines from human ESCs; that hESCs can be differentiated by allowing the cells to grow to confluence and pile up (production of embryoid bodies); that human ESCs would be valuable in studies of development and function of tissues that different between mice and humans, and that screens based upon the *in vitro* differentiation to specific lineages could identify gene targets for new drugs. The Examiner states that Thomson do not specifically teach that the embryos would have naturally occurring disease mutations, however screening of human embryos produced by IVF from various diseases was known by Harper, who provides methods to identify specific human IVF embryos that have a naturally occurring disease causing mutation. The Examiner states that neither Thomson nor Harper specifically teach the *in vitro* assay steps required by the claims, however, the '659 document teaches methods for identifying candidate agents for treating conditions associated with motor neuron degeneration by obtaining embryonic stem cells, wherein the stem cells contain a mutation in a specific gene, contacting the ESC cells with retinoic acid to differentiate

the cells into neural progenitor cells and determining the effect of an agent for use in treatment of a condition associated with motor neuron degeneration. The Examiner states that given the teachings of Thomson and Harper one of skill in the art would be able to use the methods of screening human embryos for a specific disease-causing mutation, and use those embryos in the methods taught by Thomson in order to produce isolated human ES cell lines with a naturally occurring disease-causing mutation with a reasonable expectation of success. The Examiner states that one of ordinary skill in the art would have been sufficiently motivated to make these types of ES cells in order to use then in *in-vitro* assays for identification of targets for new drugs or to analyze the molecular mechanisms of the disease by allowing the ES cells to differentiate; that it would be obvious to utilize the resultant cells in methods of screening agents suitable for treating a disorder such as the methods taught by the '659 document; that one would be motivated to make this modification in view of Thomson's teachings which suggest producing genetic modifications in ES cells, and that ES cells would be used for screening methods *in vitro* and the '659 document provide guidance to the specific steps. The Examiner further states that Elsea provide further guidance to show that various mouse models of human diseases such as metachromatic leukodystrophy, do not produce a biochemical model that reproduces clinical symptoms and therefore show a need in the art to produce cells that could be used for screening various human disease using human cells. The Examiner states that the claimed invention, as a whole is clearly *prima facie* obvious in the absence of evidence to the contrary.

Examiner's rejections are respectfully traversed.

For clarity, Applicants are describing the teachings of Thomson and Harper individually but are traversing the rejection with respect to the combination of the Thomson, Harper, US. Pat. No. 7,390, 659 and Elsea references, *infra*. That is, the Applicants are not attacking the references individually, rather addressing the combinations of references as set forth in the instant Office Action.

Applicants point that Thomson et al. teach generating human ESC lines from normal embryos (Thomson et al. Abstract) and not from embryos which carry a naturally occurring disease-causing mutation as in the claimed invention. With respect to Examiner's assertion that Thomson et al. teach that genetic modifications

could be produced in ES cells for reducing or combating immune rejection, Applicants point that these modifications are irrelevant to the present claims since they are non-natural modifications (mutations).

With respect to Harper et al., Applicants point that Harper et al. teach that pre-implantation diagnosis is performed in order to select for normal embryos, *i.e.*, devoid of mutations, which are further implanted back in the uterus for continuation of normal embryonic development, in order to achieve the birth of healthy offspring. It is clearly inferred that according to Harper et al., embryos carrying the disease-causing mutations should be discarded. Harper et al. not only do not teach or suggest using the genetically abnormal embryos for any purpose, it teaches away from the claimed invention in the sense that inferably Harper teaches discarding these the genetically abnormal embryos.

Taken together, Applicants point that a *prima facie* case of obviousness has not been properly set since Examiner has combined two references with opposing teachings. Thus, while Thomson et al., teach using human embryos for generating hESC lines, Harper et al., teach selecting against genetically abnormal embryos and using the mutation-free embryos for continuation of pregnancies with healthy embryos.

Thus, Applicants point out that one of ordinary skills in the art when combining the art of Thomson et al., who teach generating normal ESC lines from IVF embryos, in view of the art of Harper et al. who teach away from using human embryos which carry genetic mutations, in further view of US Pat. No. 7,390,659, which merely teaches methods of inducing differentiation of embryonic stem cells, or Elsea et al., who merely state that there is a need for human ESCs as a model for genetic diseases, would not have any motivation or expectation of success to generate a human embryonic stem cell line with a naturally occurring disease-causing mutation in a genomic polynucleotide thereof, methods of using same for identifying an agent suitable for treating a disorder associated with at least one disease-causing mutation, or a population of cells consisting of human embryonic stem cells carrying a disease-causing mutation in a polynucleotide thereof as in the claimed invention.

In addition, Applicants respectfully request the acknowledgment of an inventive activity based on the following secondary considerations:

1. Long felt but unresolved need – Elsea et al. (2002, cited by Examiner) establish the long felt need to generate the claimed cells. Thus, as indicated by Examiner, Elsea et al. teach that various mouse models of human diseases such as metachromatic leukodystrophy, do not produce a biochemical model that reproduces clinical symptoms and therefore show a need in the art to produce cells that could be used for screening various human disease using human cells. Thus, long felt need has been recognized by those of skilled in the art (*i.e.*, objective evidence) and not only by the present inventors.

2. Unmet need – The long felt need has not been satisfied by others before the invention by Applicants. Prior to filing the instant application there was no study which teaches or suggests using human embryos with naturally occurring disease causing mutations for establishing human ESC lines carrying such mutations in their genomic polynucleotide.

3. The invention has satisfied the long felt need – As shown in the instant application, the present inventors generated various hESC lines which carry naturally occurring disease-causing mutations for studying diseases such as cystic fibrosis (CF), myotonic dystrophy (DM), van Waardenburg syndrome (WS), metachromatic leukodystrophy (MLD), Gorlin disease, Huntington's disease (HD), spinal muscular atrophy (SMA) and Duchenne muscular dystrophy (DMD). In addition, based on the present teachings, multiple scientific studies repeated the success of the present inventors and generated additional hESC lines with disease-causing mutations (see e.g., Hoseok Song et al., 2010; Marina V Pryzhkova 2010; K. Amoroso 2008; Y Verlinsky 2005; Simon Kemp 2008; Mateizel 2006; Ileana Mateizel 2010, attached hereweith).

4. Copying of the invention by competitors – Applicants point that Stemride International Ltd. (78 Brompton Park Crescent London SW6 1SP, UK) currently sells human ESC lines carrying a disease-causing mutation as taught and described in the present claims. For further details see http://www.stemride.com/ and the attached products page from the Stemride International Ltd. web site. The establishment of such a human ESC line bank indicates that a substantial investment was made with the at least anticipated commercial success.

Taken together, it Applicants' position that since the combined art do not teach or suggest generating human ESC lines from embryos which carry naturally occurring disease-causing mutations, and based on the above described secondary considerations, an inventive step should be acknowledged.

Thomson, Harper, US. Pat. No. 7,390,659, Elsea and PGPub US 2005/0054092 A1

The Examiner has rejected claims 82-84, 96-98 under 35 U.S.C. 103(a) as being unpatentable over Thomson et al. (1998, cited previously), in view of Harper (1996, J. of Assisted Reproduction and Genetics, 13:90-95), in further view of US. Pat. No. 7,390, 659 (cited previously) and Elsea et al., 2002 (cited previously) as applied to claims 52, 55, 58-60, 74, 75, 78-80, 85, 86, 88-94, 99 and 100 above, and further in view of PGPub US 2005/0054092 A1. The Examiner states that Thomson, Harper, the '659 patent and Elsea are described above, that they do not specifically teach isolating specific cells by mechanical separation of cells, tissues and/or tissue-like structures contained within the embryoid bodies, however, the '092 document teaches suspension of pPS derived cells can be further enriched with desirable characteristics, such as mechanical separation or cell sorting, such as FACS. The Examiner states that it would have been obvious for one of skill in the art to modify the methods taught by Thomson, Harper and Elsea to include a step of isolating a lineage specific cell, utilizing either cell sorting or mechanical isolation as taught by the '092 document with a reasonable expectation of success, and that one of ordinary skill in the art would have been motivated to make this modification in order to have a purified population of cells for in vitro screening assays. Examiner's rejections are respectfully traversed.

Applicants point out that one of ordinary skills in the art when combining the art of Thomson et al. who teach generating normal ESC lines from IVF embryos, in view of the art of Harper et al. who teach away from using human embryos which carry genetic mutations, in further view of US Pat. No. 7,390,659, which merely teaches methods of inducing differentiation of embryonic stem cells, Elsea et al., who merely state that there is a need for human ESCs as a model for genetic diseases, or PGPub US 2005/0054092, which merely teaches isolation of cells, would not have

any motivation or expectation of success to generate a human embryonic stem cell line with a naturally occurring disease-causing mutation in a genomic polynucleotide thereof, methods of using same for identifying an agent suitable for treating a disorder associated with at least one disease-causing mutation, or a population of cells consisting of human embryonic stem cells carrying a disease-causing mutation in a polynucleotide thereof as in the claimed invention.

Thomson, Harper, US. Pat. No. 7,390,659, Elsea and US Pat. No. 5, 972,955

The Examiner has rejected claims 57, 81, 87 and 95 under 35 U.S.C. 103(a) as being unpatentable over Thomson et al. (1998, cited previously), in view of Harper (1996, J. of Assisted Reproduction and Genetics, 13:90-95), in further view of US. Pat. No. 7,390, 659 (cited previously) and Elsea et al., 2002 (cited previously) as applied to claims 52, 55, 58-60, 74, 75, 78-80, 85, 86, 88-94, 99 and 100 above, and further in view of US Pat. No. 5,972,955. The Examiner states that Thomson, Harper, the '659 patent and Elsea are described above, that they do not specifically teach a sequence such as those recited in claims 57, 81, 87 and 995, however, the '995 reference teaches an exact match of SEQ ID NO:24. The Examiner states that it would have been obvious for one of skill in the art to modify the teachings of Thomson, Harper and Elsea, to screen for human embryos for a specific mutation, such as the W1282X as set forth in SEQ ID NO:24 associated with cystic fibrosis and use that embryo to produce an ES cell line with a reasonable expectation of success. The Examiner states that one of ordinary skill would have been motivated to make this modification in order to produce ES cells that could then be used for screen therapeutic agents for treatment of cystic fibrosis. Examiner's rejection is respectfully traversed.

Applicants point out that one of ordinary skills in the art when combining the art of Thomson et al. who teach generating normal ESC lines from IVF embryos, in view of the art of Harper et al. who teach away from using human embryos which carry genetic mutations, in further view of US Pat. No. 7,390,659, which merely teaches methods of inducing differentiation of embryonic stem cells, Elsea et al., who merely state that there is a need for human ESCs as a model for genetic diseases, would not have any motivation or expectation of success to generate a human embryonic stem cell line with a naturally occurring disease-causing mutation in a

genomic polynucleotide thereof, methods of using same for identifying an agent suitable for treating a disorder associated with at least one disease-causing mutation, or a population of cells consisting of human embryonic stem cells carrying a disease-causing mutation in a polynucleotide thereof as in the claimed invention even with respect to SEQ ID NO:24.

Withdrawal of the rejections is respectfully requested.

Conclusion

In view of the above amendments and remarks it is respectfully submitted that claims 52, 55, 57-60, 74, 75, 78-101 are now in condition for allowance. A prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,

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